Left ventricular dysfunction in transfusion dependent beta Thalassemia major patients in Bangladesh

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Key Words : *Beta thalassemia, Iron overload, Cardiac dysfunction, left ventricular failure.*

Abstract

Background: *Thalassemia major is an inherited haemoglobin disorder resulting in chronic haemolytic anaemia. Patients with beta thalassemia major are maintained on continuous blood transfusion regimens resulting in iron overload that adversely affects both the structure and function of the heart and other vital organs which can be easily prevented with iron chelating therapy. The aim of the study was to detect left ventricular dysfunction at an early stage so that early effective intervention can be done.*

Methods: *A total of 50 patients with beta thalassemia were included in the study by non randomized qualitative purposive sampling from July 2013 to June 2014. Their total body iron status was be assessed by doing serum ferritin level. Left ventricular systolic and diastolic function was assessed by echocardiography.*

Results: *Cardiac dysfunction was present in 11 patients with high incidence in patients with low pre-transfusional haemoglobin group (p=0.4) and in patients having high serum ferritin level (p=0.02). Systolic cardiac dysfunction was present in 7(14%) of patients and diastolic dysfunction was present in 4(8%) of patients. There was a weak but significant correlation between left ventricular ejection fraction and serum ferritin concentration (r=-0.22; p=0.03). Only few (8%) patients had diastolic dysfunction.*

Conclusion: *Patients with beta thalassaemia on an adequate transfusion showed an abnormal left ventricular systolic function. In early stage of disease diastolic function was normal but after repeated transfusion there were impaired relaxation indicating diastolic dysfunction. These findings seem mainly to be related to chronic anaemia and serum ferritin level.*

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Introduction:

Thalassemia major is an inherited hemoglobin disorder resulting in chronic hemolytic anemia. WHO has estimated that about 1.5% the world's population might be carrier of â – thalassemia (â/ât) and that about 60,000 severely affected infants are born every year. These individuals mostly originate from the Mediterranean, Middle East, Central Asia, India& Southern China.[1] The estimated prevalence is 3-8% in populations from Bangladesh, China, India, Malaysia & Pakistan.[2]

Patients with beta thalassemia major are maintained on continuous blood transfusion regimens to keep hemoglobin levels close to normal and allow adequate tissue oxygenation resulting in iron overload that adversely affect both the structure and function of the heart and other vital organs.[2] Iron induced myocardial damage leads to cardiac failure, cardiac arrhythmia, sudden death, or a distressing slow death from progressive congestive cardiac failure. Treatment with iron chelating therapy in patients with beta thalassemia showed improvement of morbidity and increased survival and is considered the standard of care of this blood disorder.[3]

Echocardiographic evaluation of beta-thalassemia major patients can identify the early stages of heart disease, enabling prompt intervention.[4] However, very limited data is available about the Bangladeshi patient. A better understanding of this

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condition may provide prompt early intervention and prevention of this condition in Bangladesh.

Methods:

This cross sectional analytical study was conducted in the Dept. of Hematology and Oncology, Dhaka Medical College Hospital (DMCH) starting from July 2013 to June 2014. Beta thalassemia major patients admitted for blood transfusion were selected as study population. Sampling was done by non-randomized qualitative purposive sampling. A total of 50 patients with beta thalassemia were included in the study on the basis of following selection criteria-children suffering from beta thalassemia major diagnosed by Hb electrophoresis, age in between 4-12 years, received blood transfusion at least 10 times. Patients with other co morbid conditions (DM, ESRD), known case of congenital hypothyroidism, hyperparathyroidism and who are receiving any cardiac medication were excluded from the study.

A structured questionnaire was formed that include all the variables of interest. Their iron status was be assessed by doing serum ferritin level. Echocardiography (SIEMENS ACUSON X500 GERMANY) was performed in Paediatric cardiology department, National Institute of Cardiovascular Diseases, Dhaka. Conventional echocardiographic measurements were done according to the American Society of Echocardiography guidelines.[5] From the parasternal long-axis view of the LV end-diastolic and end-systolic diameters, interventricular septal and posterior wall thicknesses were expressed in millimeters. We measured LV end-systolic and end-diastolic (EDV) volumes from the apical 4-chamber view. Left ventricle fractional shortening (FS) and ejection fraction (EF) were measured using the Teichholz formula. LV filling was evaluated by pulse wave Doppler from the apical 4-chamber view with the sample volume position at the tips of the mitral valve, and velocities in early (E) and late (A) diastole were recorded, in addition to the calculation of the E/A ratio.

The SPSS Statistical Software (16.0 version, SPSS Inc., Chicago, Illinois, USA) was used for data analysis. Continuous variables were expressed in mean & standard deviation and categorical variables as frequency and percentage. Quantitative variables were analyzed by Student's t-test and ANOVA and Categorical variables were analyzed by chi-square test. To test association between ferritin level and left ventricular ejection fraction Pearson's correlation test used. P value of less than 0.05 was considered as significant.

Ethics

Written informed consent was taken from each patient before data collection. Confidentiality was strictly maintained and the patients were informed about the study and their rights to withdraw at any stage which would not hamper the rights to treatments. The study protocol was approved by the institutional review board of DMCH, Dhaka.

Results:

A total of 50 patients with beta thalassemia were available for analysis. The mean age of the study sample was 7.7±3.1. Most of the subjects belong to 6-10 years (50%) and 34% of patients were male. Of the 50 children with thalassemia 58% had their siblings affected. The mean age at diagnosis and at transfusion was 4.35 years. The average time interval between two consecutive transfusions was 4.3 months. About 20% children used chelating agent. The mean duration of transfusion was almost 6 years and the average number of transfusions was 23. The average serum ferritin level was 1280 ng/ml. [Table I]

Table I

Baseline characteristics of the study participants (n=50).

Variables	Mean	Range
Male	34(68%)	
Age (years)	7.7±3.1	2-12
Thalassaemia diagnosed at age (years)	4.35 ± 1.73	1-7
Blood transfusion started at age (years)	4.35 ± 1.73	1-7
Interval between two consecutive transfusions (months)	4.3 ± 1.2	1-6
Pre transfusion haemoglobin (gm/dl)	7.48±1.65	6.3-9.1
Chelating agent used [Frequency (%)]	10 (20%)	
No. of transfusions received so far	23.0 ± 4.0	
Serum ferritin level (µml/l)	1280±316	

Regarding systolic left ventricular function average ejection fraction was 65%, 7(14%) patients had reduced ejection fraction (<55%) among them some have increased ventricular volume. Average fractional shortening was 29%, however in some patients it is also reduced. Diastolic function parameters by color Doppler imaging shows average E/A ratio 1.53 and Deceleration time was 104 milliseconds. 4(8%) patients have impaired diastolic relaxation and function (E/A ratio<1). [Table II]

Table-II

Echocardiographic Variables of the study participants (n=50).

Variables	Mean	Range
Systolic Function		
IVSd (mm)	5.9±1.7	5.0-9.3
PWDd (mm)	6.1±1.3	4.9-8.7
LVIDd (mm)	34±3.7	29-41
LVIDs (mm)	24±2.9	20-29
FS (%)	26±4.8	20-35
EF (%)	58±11.7	47-71
Diastolic Function		
E (cm/s)	93±13	68-137
A (cm/s)	42±9	28-67
E/A	1.53±0.52	0.7-2.24
DT (ms)	104±9	89-117

In this study there were 11 patients had cardiac functional abnormalities; 7 of them had systolic function abnormalities (EF<55%) and 4 had diastolic function abnormalities (E/A ratio<1), when we correlate this cardiac dysfunction with haemoglobin and ferritin level we found cardiac functional abnormalities more frequently associated with anaemia and significantly associated with elevated ferritin level (p=0.02)[Table III]

Table-III

Cardiac dysfunction according to Haemoglobin and Ferritin (n=50).

Parameter	Cardiac dysfunction		p value
	Present	Absent	
Haemoglobin			
<6	7	20	0.40^{ns}
6 – 9	4	19	
Ferritin			
<1000	3	26	0.02^{s}
>1000	8	13	

*ns=not significant. s=significant. chi square test used to determine significance

Among all the hematological data considered, only the serum ferritin concentration showed a weak negative correlation with the left ventricular ejection fraction (r = -0.22; p < 0.05) [Figure 1]

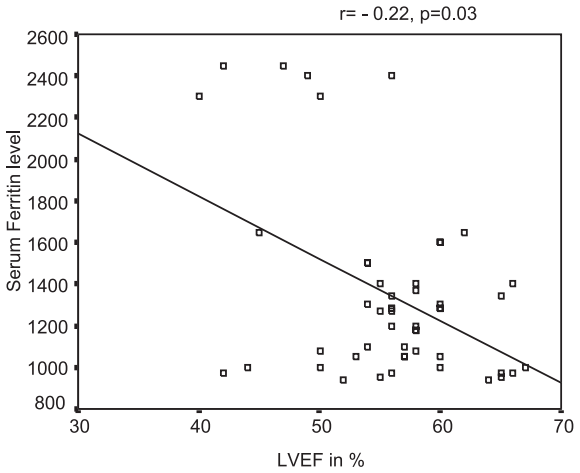

Fig.-1: *Correlation of serum ferritin level with ejection fraction (n=50).*

Discussion

The present study showed that cardiac dysfunction was present in 11 patients; systolic cardiac dysfunction present in 7(14%) of patients and diastolic dysfunction present in 4(8%) of patients, with high incidence in patients with low pre transfusional haemoglobin group (p=0.4). Anaemia is a contributing factor for cardiac dysfunction in thalassaemic patients, abnormal cardiac function was higher in patients with anaemia of moderate severity, and although statistically not significant it indicates a positive correlation between severity of anaemia and cardiac dysfunction. This finding is consisted with Kremastinos et al.[6]

Cardiac dysfunction occurring more frequently in patients having high serum ferritin level (p=0.02). This findings supported by several other similarly designed studies conducted by Shikow et al,[7]Bosi et al,[8]Noori et al.[9] Quality and duration of life of thalassaemic patients can be expected now to extend beyond the 3rd decade with regular blood transfusion and iron chelating therapy. Cardiac complications is still a major problem in the management of these patients as a consequence of chronic iron overload can result from transfusional iron overload, increased intestinal absorption of iron and also from ineffective erythropoiesis.[10] Within the heart, changes

associated with chronic anaemia which is aggravated by iron deposition. Excessive iron deposition associated with cardiac hypertrophy and dilatation, degeneration of myocardial fibers and in rare cases fibrosis. In patients who are receiving transfusion but not chelating therapy symptomatic cardiac disease has been reported within 10 years after the start of transfusion.[11-13]

In our study, we found a weak but significant correlation between left ventricular ejection fraction and serum ferritin concentration (r=-0.22; p=0.03). Patients with a high ferritin concentration (> 1000 ng/ml) had a lower ejection fraction than patients with a low ferritin concentration (< 1000 ng/ml). In 1994 Olivieri and colleagues, in a prospective clinical study, found that the cardiovascular prognosis in thalassaemic patients was excellent if serum ferritin concentrations were maintained below 2500 ng/ml. This value has been considered a "safe" concentration.[14] Our study confirms this assumption, demonstrating the importance of a low ferritin concentration for the preservation of left ventricular mechanics. This probably reflects a more aggressive treatment and the further lowering of the ferritin concentration in our study population. Our study suggests that a serum ferritin value of less than 1000 ng/ml should be considered the ideal goal of any therapeutic schedule and in 2003 Bosi and colleagues also reported this.[8]

Reports concerning left ventricular diastolic function in patients with beta thalassemia are somewhat normal. Only few patients had diastolic dysfunction. In 1991, Spirito and colleagues reported a restrictive pattern of trans-mitral flow in a group of young adults with normal systolic function.[9] In contrast, no alteration in left ventricular compliance was reported in the early stage of the disease by Kremastinos and associates.[10,15] In agreement with Kremastinos and colleagues,[10] we have shown in our group of asymptomatic thalassaemic children that there is normal left ventricular compliance.

Limitation of the study

However, like other scientific study this present study is not without limitation.The present study was conducted on a small number of cases and as such the study findings cannot be generalized to reference population.Analysis of left ventricular diastolic function assessed diastolic filling which is not always equivalent todiastolic function. Number of blood units transfused has not been shown conclusively to be an accurate index of iron overload, since iron turnover and iron absorption are increased in beta thalassemia major, and in addition, iron chelation therapy decreases the amount of deposited iron. Serum ferritin cannot accurately estimate the iron content is higher in the heart.

Conclusion:

This is the first study to present the cardiac dysfunction related to repeated transfusion among beta Thalassaemia patients in Bangladesh. Patients with beta thalassaemia on an adequate transfusion showed an abnormal left ventricular systolic and diastolic dysfunction which is mainly related to chronic anaemia and serum ferritin level. It may be recommended that echo-1cardiographic assessment should be routinely done in beta thalassaemia patient on transfusion specially those with serum ferritin concentration more than 1000 ng/ml. Standard chelation treatment should be given to preserve cardiac and other vital organ function.

Conflict of Interest - None.

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